1,3-BUTADIENE
(Group 2A)

For definition of Groups, see Preamble Evaluation.

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Butadiene

CAS No.: 106-99-0
Chem. Abstr. Name: 1,3-Butadiene

Diepoxybutane

CAS No.: 1464-53-5
Chem. Abstr. Name: 2,2′-Bioxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,3-Butadiene is a monomer used in high volume in the manufacture of a wide range of polymers, including styrene–butadiene rubber, polybutadiene, nitrile rubber, acrylonitrile–butadiene–styrene resins and styrene–butadiene latexes. It is also an intermediate in the production of various other chemicals.

Occupational exposure to 1,3-butadiene occurs in the production of monomeric 1,3-butadiene and of 1,3-butadiene-based polymers and 1,3-butadiene-derived products. The mean full-shift, time-weighted average exposure levels measured for workers in these industries have usually been below 10 ppm [22 mg/m^3], although that level may be exceeded during some short-term activities. Recent data from monomer extraction and styrene–butadiene rubber plants showed lower average concentrations (< 5 ppm [< 11 mg/m^3]. 1,3-Butadiene is not usually found at detectable levels in workplace air during manufacture of finished rubber and plastic products.

The general population may be exposed to very low levels of 1,3-butadiene due to its occurrence in engine exhausts and cigarette smoke.

5.2 Human carcinogenicity data

One cohort study of workers in the United States who manufactured 1,3-butadiene monomer showed a moderate and significant excess of lymphohaematopoietic cancers based on 42 deaths. Persons employed before 1950 were especially at increased risk, but there was no convincing association with a cumulative exposure score. A total of 13 leukaemia cases only slightly and insignificantly contributed to the excess of the lymphohaematopoietic cancers.

A small cohort study of 1,3-butadiene production workers showed a significant excess of

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lymphosarcoma and reticulosarcoma, based on four cases. There was also an excess of stomach cancer, although represented by only five cases. Two leukaemia cases were found: this was slightly more than expected.

Several reports have been published on follow-up of styrene–butadiene rubber workers at eight plants in the United States and Canada. The most recent follow-up showed a consistent excess of leukaemia and a significant dose–response relationship with cumulative exposure to 1,3-butadiene, which remained after adjustment for exposure to styrene.

Evaluation of the human carcinogenicity of 1,3-butadiene hinges on evidence regarding leukaemia risks from one large and well conducted study and two smaller studies. The smaller studies neither support nor contradict the evidence from the larger study. The larger, United States–Canada study shows that workers in the styrene–butadiene rubber industry experienced an excess of leukaemia and that those with apparently high 1,3-butadiene exposure had higher risk than those with lower exposure. The evidence from this study strongly suggests a hazard, but the body of evidence does not provide an opportunity to assess the consistency of results among two or more studies of adequate statistical power. Further, while 1,3-butadiene was a major exposure in this cohort, there were others, and it remains possible that even if there is an increased risk of cancer in the styrene–butadiene rubber industry, it may be due to occupational exposures other than 1,3-butadiene.

5.3 Animal carcinogenicity data

1,3-Butadiene was tested for carcinogenicity by inhalation exposure in four experiments in mice and one experiment in rats.

In the studies in mice, tumours were induced in multiple organs at all exposure concentrations studied, ranging from 6.25 to 1250 ppm [13.8–2760 mg/m^3]. The tumours induced included malignant lymphomas and heart haemangiosarcomas. Neoplasms at multiple organ sites were induced in mice after as little as 13 weeks of exposure at exposure levels of 625 ppm.

In one inhalation study in rats, 1,3-butadiene increased the incidence of tumours at several sites. The tumour increases were mainly in organs in which tumours develop spontaneously. The response was seen mainly at 8000 ppm [17 700 mg/m^3].

The initial metabolite of 1,3-butadiene, 1,2-epoxy-3-butene, yielded equivocal results in carcinogenicity tests, whereas the subsequent metabolite, 1,2:3,4-diepoxybutane, was carcinogenic to mice and rats when administered by skin application or by subcutaneous injection.

5.4 Other relevant data

1,3-Butadiene is metabolized in experimental animals and human liver microsomes to epoxide metabolites, initially 1,2-epoxy-3-butene and subsequently 1,2:3,4-diepoxybutane, by cytochrome P450. The epoxides can be inactivated by epoxide hydrolase and glutathione *S*-transferases. Adducts formed by reaction of 1,2-epoxy-3-butene and 3,4-epoxy-1,2-butanediol with haemoglobin and urinary mercapturic acids derived from 1,2-epoxy-3-butene have been detected in 1,3-butadiene-exposed workers. There are significant species differences in the metabolism of 1,3-butadiene both *in vitro* and *in vivo*. The in-vitro data are consistent with modelled and measured concentrations of 1,2-epoxy-3-butene and 1,2:3,4-diepoxybutane in 1,3-butadiene-exposed mice and rats. In these animals, blood and tissue levels of 1,2-epoxy-3-butene are several times higher in mice than in rats and those

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of 1,2:3,4-diepoxybutane up to 100 times higher in mice than in rats. There is considerable interindividual variability in the ability of human liver microsomes to metabolize 1,3-butadiene and 1,2-epoxy-3-butene *in vitro*. Mechanistic data suggest that the much higher carcinogenic potency of 1,3-butadiene in mice than in rats results predominantly from the high burden of 1,2:3,4-diepoxybutane.

The haemoglobin-binding index of 1,2-epoxy-3-butene can be considered as a dose surrogate for this metabolite; corresponding haemoglobin-binding indices have been published for mouse and rat. Haemoglobin-binding indices in occupationally exposed humans have also been estimated. In agreement with model predictions, these data demonstrate binding indices for 1,3-butadiene-exposed humans more than one order of magnitude lower than those in exposed rats.

There are conflicting results on whether 1,3-butadiene increases *hprt* mutations in lymphocytes from 1,3-butadiene-exposed humans compared with non-exposed controls. Sister chromatid exchanges, micronuclei, chromosomal aberrations and DNA strand breaks were not significantly elevated above control levels in peripheral blood lymphocytes of occupationally exposed workers. 1,3-Butadiene induced DNA adducts and damage in both mice and rats *in vivo*, although the damage was significantly greater in mice than in rats. 1,3-Butadiene is mutagenic in virtually all test systems both *in vitro* and *in vivo*. Where a direct comparison between rats and mice could be made for the same end-point, positive effects were observed primarily in mice.

Activated K-*ras* oncogenes have been detected in lymphomas and in liver and lung tumours induced in mice by 1,3-butadiene. Mutations in the *p53* tumour-suppressor gene have been detected in mouse lymphomas.

1,2-Epoxy-3-butene was directly mutagenic in bacteria and induced gene mutations, chromosomal aberrations and sister chromatid exchanges *in vivo* in rodents. Micronuclei were induced in both somatic and germ cells of mice and rats *in vivo*. It induced gene mutations and sister chromatid exchanges in cultured human lymphocytes but did not induce unscheduled DNA synthesis, micronuclei or chromosomal aberrations in mouse or rat cells *in vitro*.

1,2:3,4-Diepoxybutane is a potent bifunctional alkylating agent which reacts with DNA *in vitro* and *in vivo*. As a result, it is mutagenic in virtually all test systems including effects in somatic and germ cells of mammals exposed *in vivo*. *In vivo*, it induced DNA adducts, dominant lethal mutations and gene mutations in mice; chromosomal aberrations and sister chromatid exchanges in Chinese hamsters and mice; and micronuclei in splenocytes and spermatids of rats and mice. It induced gene mutations, chromosomal aberrations and sister chromatid exchanges in human and mammalian cell cultures. In one study, 1,2:3,4-diepoxybutane induced DNA–DNA cross-links in murine hepatocytes *in vitro*. It induced somatic and sex-linked recessive lethal mutations, chromosomal deletions and heritable translocations in *Drosophila*. Gene mutations were induced in bacteria in the mouse host-mediated assay and *in vitro*. 1,2:3,4-Diepoxybutane also induced bacterial prophage and DNA repair.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of 1,3-butadiene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,3-butadiene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2:3,4-diepoxybutane.

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Overall evaluation

1,3-Butadiene is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluations: Butadiene: Vol. 39 (1986); Suppl. 7 (1987); Vol. 54 (1992); diepoxybutane: Vol. 11 (1976); Suppl. 7 (1987)

Synonyms

Butadiene

- Biethylene
- Bivinyl
- 1,3-Butadiene
- Buta-1,3-diene
- α,γ-Butadiene
- *trans*-Butadiene
- Divinyl
- Erythrene
- Pyrrolylene
- Vinylethylene

Diepoxybutane

- Butadiene dioxide
- 1,2:3,4-Diepoxybutane

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